**REMARKS**

Reconsideration and allowance are respectfully requested.

Claims 6, 13, 16-18, 25, 29-30 and 34-38 are pending.

*35 U.S.C. 103 – Nonobviousness*

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The Graham analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. But a claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 6, 13, 16-18, 25, 29-30 and 34-38 were rejected as allegedly unpatentable over Bertilsson et al. (US 2003/0165485) in view of Hung (US 2003/0060415). Applicants traverse.

Bertilsson discloses the "potential therapeutic use" of protein S signaling in a method of influencing adult neural stem cells and progenitor cells to produce progeny. Thus, the document specifically teaches that the desired result is producing progeny

cells that will replace or supplement the cells lost to disease. See, for example, paragraphs [0018] to [0021]. The document does not contain any explicit or implicit teaching that administration of protein S to a subject would provide neuroprotection as required by Applicants' claim 6 because the present invention relies on the effect of protein S on preventing cell death or apoptosis.

The '485 application does not make obvious the present claims. Specifically Bertilsson's examples contain data showing expression of Reelin and its receptors, Gas6 and its receptors, in vitro experiments to define the therapeutic potential of Gas6 and its receptors, the production and purification of human Gas6, and in vivo analysis of Gas6's effect on neural proliferation. But they are silent on neuroprotective activity of protein S. One of ordinary skill in the art would not readily accept Bertilsson's argument in paragraph [0061] that Gas6 and protein S could serve as functional equivalents:

> Interestingly, Gas6 displays significant amino acid sequence identity to Protein S, an additional member of the vitamin K-dependent family and an important co-factor in the inhibition of the blood coagulation cascade, suggesting possible functional similarities between these two proteins (Manfioletti et al., 1993). In support of this model, Protein S has been proposed to serve as an additional ligand for Tyro3 (Stitt et al., 1995).

The skilled artisan would have been aware of the art-known rejection of this concept that protein S would have the same biological activities as Gas6. For example, Nagata et al. (J. Biol. Chem. 271:30022-30027, 1996) reported:

> Although Stitt et al. reported that human or bovine protein S bound to murine Sky (Tyro3), intraspecies (human-human) ligand-receptor interactions of protein S and Sky could not be detected (Ohashi et al., 1995; Godowski et al., 1995). Hence, it is probable that Gas6, but not protein S, is a ligand for Sky, and Gas6 may also be a common ligand for Axl and Sky, two related receptors.

Nagata et al. (1996) also concluded:

> The inability of intraspecies (human-human) ligand-receptor interactions between protein S and Sky suggested that protein S could not function as a natural ligand for Sky. Thus, Gas6, but not protein S, seems to be the ligand for the two related receptors, Axl and Sky.

Thus, the skilled artisan would have known of the contradictory scientific literature and their teachings that it would not have been obvious in the art to use protein S and Gas6 as functional equivalents for their biological activities as alleged by Bertilsson.

The Examiner acknowledged that "there had been some controversy in the mid-1990s as to whether or not protein S activates Sky" (page 4 of the Office Action mailed December 30, 2009). He cited Lan et al. (Blood 95:633-638, 2000) for showing Tyro3/Sky is activated by protein S. Lan expressed rat Tyro3 in mouse NIH3T3 cells. Tyro3 is a receptor tyrosine kinase having the following: an extracellular ligand-binding domain, a single transmembrane domain, and a cytoplasmic domain. The cytoplamic domain interacts with the p85 subunit of PI3 kinase (also see the table on page 635). Treatment of Tyro3-transfected NIH3T3 cells (cultured in 10% serum) with 5 μM of human protein S resulted in increaseed phosphorylation of Akt, which is a downstream component of the PI3 kinase signaling pathway (Fig. 7 and page 637). But no direct interaction was shown between protein S and Tyro3. Moreover, an alternate treatment with 20% serum mimicked the phosphorylation result obtained by treatment with protein S. It was stated that Nyberg et al. (Eur. J. Biochem. 246:147-154, 1997) suggests that "protein S may function as a Tyro3 ligand at least in some species" (page 638). Lan concluded, "Our current study also confirmed that interspecies ligand-receptor interaction occurs between protein S and Tyro3" (emphasis added). The authors did not conclude that human protein S would act as a ligand for human Tyro3. Therefore, Lan fails to support what is being alleged in the Office Action: there is no evidence that human protein S and human Sky interact as ligand and receptor. The complicated culture system used in Lan does not permit one of ordinary skill in the art to make any conclusion about direct ligand-receptor interactions.

Therefore, one of ordinary skill in the art would not found obvious the neuroprotective activity of protein S as discovered and claimed by Applicants because protein S and Gas6 are not functionally equivalent for the biological activity of activating Sky. The evidence as a whole does not support Bertilsson's contention that protein S would have all of Gas6's biological activities (including Sky activation).

One of ordinary skill in the art would also have no reasonable expectation from the evidence of record that Applicants' claimed neuroprotection of cells or effective treatment after neurotrauma and stroke would be achieved in a subject without also administering protein C or activated protein C (APC).

By contrast, Fig. 5 of Applicants' specification demonstrates that protein S will act directly on neural cells to protect them from cell death or apoptosis. In an animal model of neuroprotection using 12 hours of hypoxia/aglycemia (also known as oxygen glucose deprivation, OGD) followed by 12 hours of re-oxygenation (normal oxygen content and normal glucose content), which is accepted as a valid in vitro model of neuronal ischemia and stroke (see page 26, lines 6-15, of the specification), both plasma-derived and recombinant protein S were shown to exert time-dependent and dose-dependent direct effects as a neuroprotective agent. None of this was shown by Bertilsson.

In Applicants' specification at page 26, lines 16-26, human protein S is taught to act as a cell survival factor for human brain endothelial cells in another in vitro model of oxidant stress. These results show that protein S may also be vasculoprotective. Thus, without being bound to any specific mechanism of action for the neuroprotection that is achieved by administering protein S, such vasculoprotection might be important for the overall neuroprotection that provides a beneficial effect(s) after neurotrauma or stroke. None of this was shown in Bertilsson. The cited document contains no example of direct neuroprotection, or even cerebral vasculoprotection, that is an essential feature of Applicants' invention of administering protein S to a subject.

It was known in the art that agents promoting neurogenesis (for example, stroke-induced neurogenesis as discussed by Bertilsson) are not necessarily neuroprotective. Zhang et al. (Stroke 33:2675-2680, 2002) show that sildenafil will robustly affect post-stroke neurogenesis and promotes functional recovery related to neurogenesis, but it is not neuroprotective and does not reduce brain infarction after stroke. Similarly, statins (Chen et al., Ann. Neurol. 53:743-751, 2003) and erythropotein (Wang et al., Stroke 35: 1732-1737, 2004) can importantly enhance post-ischemic angiogenesis and neurogenesis, but are not neuroprotective and do not reduce brain infraction after stroke. Therefore, from Bertilsson's disclosure, one of ordinary skill in the art would not conclude that it would have been obvious with a reasonable expectation of success for agents that promote neurogenesis to be neuroprotective agents too. Neurogenesis and neuroprotection are two distinct processes as acknowledged by skilled artisans.

Hung discloses the treatment of coronary conditions and cardiovascular indications, which were defined as referring to a diagnosis or presumptive diagnosis of cardiovascular disease and to a condition that affects the heart (paragraph [0070]). The document refers to "treatment" as the treatment of cardiovascular disease (see paragraph [0071]). Hung does not refer to treatment of the brain or prevention of neural cell death. Therapeutic agents (e.g., protein S) are specifically taught to be directly delivered into the pericardial space. The cited document does not contain any explicit or implicit teaching that administration of human protein S to a human subject would provide neuroprotection as required by Applicants' claim 6 because the present invention relies on the effect of protein S in the brain. As regards Applicants' claims 25 and 30, there was no disclosure in Hung that treatment of neurotrauma or stroke would be achieved without also administering protein C or APC. Nowhere in Hung was it taught or even suggested that no protein C or APC is administered, there is no deficiency of protein S activity in the subject, or any of the recited results of treatment could be achieved with a reasonable expectation of success.

Finally, the present claims are not obvious over Hung because it teaches away from Applicants' claimed invention by limiting the invention disclosed in the '415 application to delivery of the therapeutic agent to the pericardial space. Applicants' claims do not require delivery of human protein S to the patient's pericardial space.

These deficiencies of the Bertilsson and Hung documents are not remedied by combining them. Alone or in combination, the cited documents fail to teach or suggest any beneficial effect of administering protein S on neuroprotection when no protein C or APC is administered to a subject. Bertilsson relates to the beneficial effect of protein S on neural stem cells and neural progenitor cells, not differentiated neural cells. Hung is concerned with the treatment of coronary and cardiovascular conditions, instead of the cell death or apoptosis in the nervous system that is prevented by using Applicants' invention. Specifically, the cited documents contain no disclosure of using protein S to provide neuroprotection (claim 6), to treat neurotrauma (claim 25), or to treat stroke (claim 30) as required by Applicants' invention. There was also no reasonable expectation that administration to a human subject of human protein S would provide "neuropro-

tection after brain injury caused by at least cerebral ischemia, hypoxia, re-oxygenation, or a combination thereof" (claim 6), an effective treatment after neurotrauma (claim 25), or an effective treatment after stroke (claim 30). Further, the cited documents contain no reasonable expectation that those beneficial results would be achieved without administering protein C or APC.

Bertilsson and Hung fail to disclose or make obvious a method of treatment using human protein S that does not also administer protein C or APC. It also would not have been obvious to treat human subjects in accordance with Applicants claimed invention when such patients had no deficiency of protein S activity (dependent claims 13, 29 and 34). Moreover, none of the results of the claimed method of treatment recited in dependent claims 17-18 and 35-38 would have been obvious to one of ordinary skill in the art when the claimed invention was made. Therefore, the present claims are not obvious over Bertilsson and Hung.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

*Conclusion*

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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